REMARKS

Applicants again want to thank the Examiner for the courtesy of conducting an interview with applicants' representative on October 7, 2008. As indicated in the Interview Summary, claims 1, 4, 5, 8-10, 15 and 19 were discussed. The reference WO99/33448 was also discussed.

Claims 1, 2, 4, 5, 8-11, 15, 19, and 25-30 are in this application.

Claims 1, 2, 4, 11, and 25-30 have been amended to include the term "once-a-day". Support for this amendment is found at least on page 1, line 21; page 4 and page 6 of the application.

Claim 5 has also been amended and support for the amendment to claim 5 is found on page 10 of the application.

Claim 10 has also been amended and support for the amendment to claim 10 is found on page 11 of the application second full paragraph on page 10 of the specification ("Preferably the composition also comprise release modifiers.") and in original claim 10.

According to the action, claims 4, 5, 7-10, 15 and 19 are rejected under 35 USC 112, first paragraph because of the term "combination" in these claims. As discussed during the interview, the term "combination" is not used in claims 4, 5, 8, 10, 15 and 19. Claim 7 was cancelled previously. Therefore, it is respectfully requested that this rejection be withdrawn.

According to the action, claim 9 is rejected under the 35 USC 112, first paragraph because the term "acidic substance" in claim 9, line 5 presents new matter. This is respectfully traversed.

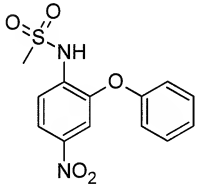
It is applicants' position that the use of the phrase "acidic substance" in claim 9, does not present new matter. The compounds hydrochloric acid, citric acid, fumaric acid, malic acid, maleic acid, ascorbic acid and tartaric acid that appeared after the phrase "acidic substance" in the prior version of claim 9 are all acids, e.g. an acidic substance. However, to expedite

prosecution, claim 9 has been amended to delete the phrase "acidic substance." Support for the addition of the phrase "release modifier" to claim 9 is found, as discussed during the interview in the second full paragraph on page 10 of the specification ("Preferably the composition also comprise release modifiers."). A description of examples of release modifiers is found starting in the middle of page 10 (Suitable example of such ingredients include :) to the middle of page 11.

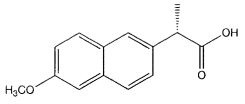
It is therefore respectfully requested that the rejection of claim 9 be withdrawn.

On page 3 of the Office Action it is stated that claims 1, 2, 4, 5, 8-11, 15, 19, and 25-30 are rejected under U.S.C 103 (a) as being unpatentable over Saslawaski et al. (WO99/33448) in view of Gibson et al. (US 6426340; 7/30/02). This is respectfully traversed.

Nimesulide is not disclosed in WO99/33448. Although naproxen is disclosed in the reference, naproxen and nimesulide are different active agents. As shown below the structures of two compounds are chemically distinct:



Chemical Structure of Nimesulide



Chemical structure of Naproxen

Naproxen is a member of the 2-arylpropionic acid (profen) family of NSAIDs. It is an odorless, white to off-white crystalline substance. It is lipid-soluble and practically insoluble in water. While nimesulide, chemically 4'-nitro-2'-phenoxy methane sulfonanilide, is a weakly acidic non-steroidal anti-inflammatory drug which is sparingly soluble in water. It differs from other non-steroidal anti-inflammatory drugs (NSAIDs) in that its chemical structure contains a sulfonanilide moiety as the acidic group rather than a carboxylic group. It exhibits a significant selectivity toward cyclooxygenase-2 (COX-2) versus COX-1 inhibition, which may explain the lower incidence of gastric side effects. Therefore, it is clear that the both the compounds naproxen and nimesulide are chemically distinct to each other and behave differently.

Furthermore, the active substances disclosed in WO 99/33448 have different physico-chemical properties; some are soluble, some insoluble, some show pH-dependent solubility and some do not (See page no. 4, line nos. 17-38 to page 8, line 29 of the cited publication). The substances have different physico-chemical properties such as solubility, effective dose, pKa, permeability, etc. and hence require specific formulation strategies in terms of nature and quantity of excipients used and/or process parameters. For example among NSAIDs, diclofenac sodium as disclosed in WO99/33448 has high aqueous solubility and is easy to formulate.

In addition, the NSAIDs on page 5, lines 6-21 are described as arylpropionic derivatives, arylacetic derivatives, anthranilic derivatives, indole derivatives, oxicams, pyrazole-containing derivatives and indene derivatives. Sulfonanilides as a class are not included in this list.

Hence, different active substances with different properties cannot have the same generalized formulation as disclosed in the cited publication. Nimesulide is practically insoluble in water and difficult to formulate. (See WO 91/17774 -Page no. 1, Second Paragraph lines 6-20, especially line No. 15-20 of the same paragraph); WO 99/41233 (Page no.1, second paragraph lines 6-12, especially line no. 9-12 of the same paragraph.); Nalluri, B.N. et al., AAPS PharmSciTech 2003; 4(1) Articles 2 (Page no. 1 second column under heading "INTRODUCTION" line 12-25); and Piel, G., Pirotte, B., Delneuville, I. et al "Study of the influence of both cyclodextrins and L-lysine on the aqueous solubility of nimesulide; Isolation and characterization of nimesulide-L- lysine-cyclodextrin complexes"; Journal of Pharmaceutical Sciences Volume 86, Issue 4, April 1997, Pages 475-480.)

The present invention provides a formulation specifically for nimesulide which is a poorly water soluble active substance along with release controlling materials.

As discussed above, the claims have been amended to define the composition as a once-a-day controlled release pharmaceutical tablet composition. . The composition of the present invention comprises a single unit fast release layer and a single unit extended release layer wherein nimesulide, from the fast release layer, provides immediate benefit to the patient and from the extended release layer, provides benefit to the patient for a longer duration.

WO99/33448 does not disclose nor suggest a once-a-day controlled release composition.

For example, Example 1 of WO9933448 discloses that Eudragit® is used in concentration of 8.80% and Example 3 of the cited reference discloses that Eudragit® is used in concentration of 10, 8.8 and 8.8% (page no. 20, line nos. 22 to 27; page no. 23, line nos. 26 to 31; page no. 24, line nos. 1 to 14 of the cited publication)]. Figures 1-6 all show dissolution in 9 hours or less.

The material used in WO99/33448 is not sufficient to prolong the release of active substance for a considerably longer duration of time; thus it does not provide any teaching about once-a-day composition of nimesulide. Therefore the formulation disclosed in the PCT publication cannot be considered as prolonged release formulation in the true sense.

Moreover, the cited publication does not provide any suggestion or motivation by means of any composition for the one skilled in the art to replace an active drug described in the reference with nimesulide to prepare a controlled release pharmaceutical tablet composition of nimesulide consisting of a single unit fast release layer and a single unit extended release layer to provide once-daily dosing of nimesulide; especially given the problems discussed above associated with preparing a formulation of nimesulide.

The combination of WO99/33448 and US Patent 6426340 B1 (Gibson et al.) does not make the claimed invention obvious. US Patent 6,426,340 discloses silicon dioxide as a common excipient used in immediate and controlled release tablet formulation. It does not teach multilayered or bilayered tablet of nimesulide as claimed in this invention.

As there is no suggestion or motivation in either of the cited references or in the combination of the references to develop a once-a-day controlled release composition of nimesulide and in addition, there is no reasonable expectation of success to obtain the applicant's invention, it is clear that the claimed invention is patentable over these references.

The nonobviousness of the claims is further supported by the law.

Following KSR, the Federal Circuit may find a claim obvious if the prior art points in the general direction of the invention (thereby arguably making it obvious to try) **and** those skilled in the art would believe that what was pointed to by the prior art would have a reasonable expectation of success.

In this case, the cited references do not point in the general direction of a once-a-day controlled release pharmaceutical composition and given the disclosure in the references and the known difficulties in formulating nimesulide, there is no reasonable expectation of success based on the cited references.

The analysis of whether a claim is obvious is based on the Supreme Court's decision in **Graham v. John Deere**, 383 US 1, 148 USPQ 459 (1966). The court stated:

> While the ultimate question of patent validity is one of law, the section 103 condition,...lends itself to several basic factual inquiries. Under section 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

To establish a prima facie case of obviousness, three basic criteria must be met. (MPEP 076.02 (j)). First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure.

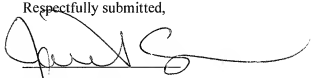
In the present case, there is no suggestion of a once-a-day formulation of nimesulide; no reasonable expectation of success in formulating a once-a-day tablet composition of nimesulide and all of the claim limitations (e.g. once-a-day tablet composition) are not disclosed in the reference.

A once-a-day formulation solves a long-felt need for a once-a-day tablet composition of nimesulide. The difficulties in developing a once-a-day tablet composition of nimesulfide were discussed above.

Therefore, as the claims are not obvious over the combination of WO99/33448 and Gibson, it is respectfully requested that the rejection of claims 1, 2, 4, 5, 8-11, 15, 19, and 25-30 be withdrawn.

Accordingly, it is submitted that the present application is in condition for allowance. If there any outstanding issues, it is respectfully requested that the Examiner contact the undersigned by telephone.

Respectfully submitted,



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